have been reviewed in detail[4] and recently summarized.[5] Referring to the occupational studies, Pool says, "Individually, the various epidemiological studies can each be challenged on one ground or another, but as a group they have a rough consistency that is hard to ignore."[5] Thus, these studies illustrate the inherent difficulty of conducting research on the possible health effects of long-term, low-level exposure. As noted in the epitome, the methodologic concerns need to be addressed in better-designed studies, rather than regarding them as fatal flaws that preclude further investigations. Further credible research to understand any relationship of electric magnetic field exposures and adverse health effects is thus supported and encouraged.[5]

The claims that have been published regarding electromagnetic fields and cancer should not be characterized as "unsubstantiated," as the methodology of studies with both positive and negative results can be and have been criticized.[5] This will always be true because human studies do not—and ethically should not—deal with randomized controlled experiments to assess the relationship. Other causal associations (such as that of smoking and lung cancer) have been elucidated, even though their exact pathophysiologic mechanism(s) was not well understood at the time the association was affirmed.[2] This has not precluded developing and implementing effective preventive measures when the bulk of the evidence supports a causal association. If and when an excess risk of childhood cancer with electromagnetic field exposure is firmly established, it must also be determined to be a causal association, an endpoint that is not always clear-cut. Indeed, Rose points out that certainty and proof are inappropriate measures on which to base policy concerning public health: "Lack of proof is not in itself sufficient objection to action. . . ." He goes on to say, "direct observations of evident health effects should take priority over theoretical expectations,"[2] and, one might add, particularly when those health effects have potentially devastating outcomes.

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Third World Plastic Surgery

To the Editor: In the last several years, an exponential growth has occurred in the quality and quantity of overseas charitable programs. It is estimated that 20% of plastic surgeons have donated their time and skills without charge to those in developing countries unable to receive care.[1] Specialists in orthopedics, ophthalmology, anesthesia, and maxillofacial surgery also participate heavily in these activities.

In plastic surgery, perhaps 400,000 operations have been done. With more than one surgical procedure per patient, almost 200,000 lives have been improved substantially. World relations have not suffered with this effort. Indeed, the hypothesis is that one person helping another is the best form of diplomacy extant in the world today.

Individual surgeons explain that the objectives of these programs are to provide an opportunity to help people, share knowledge with others, and form new professional relationships. Typically, participants say that the interchange challenges their full spectrum of training. Physicians feel as though they function as "real doctors" and are renewed in their excitement about their specialty.

Interplast, Reconstructive Surgery Foundation, African Medical Research and Educational Foundation (AMREF), Physicians for Peace, Operation Smile International, Interface-UCSD, Austin Smiles, Operation Rainbow, Operation Kids, Northwest Medical Team, and Southwest Medical Teams' Project Huasteca are some of the privately sponsored plastic surgery organizations dedicated to helping children who are not as fortunate as those in developed countries. The Plastic Surgery Education Foundation maintains a data base of volunteer organizations (call Andrea Contreras at 708-228-9900).

A child with a cleft lip or palate may be a pariah in the community, but a plastic repair may change a child who has little or no educational or social opportunity into a productive citizen. Our greatest goal is to see the recipients of our care become actual dispensers of care to other persons. "Give a boy a fish, he will enjoy a nice meal; teach him to fish, and he will not be hungry the rest of his life."[2] *Los barcos son seguros en los puertos; pero no fueron hechos para estar allí* ("The ships are safe in the harbors, but they weren't made to be there."[3] Doctors are comfortable at home, but they are trained to help people.)

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Tryptophan and Eosinophilia-Myalgia Syndrome

To the Editor: In "Tryptophan-Induced Eosinophilia-Myalgia Syndrome" in the September issue,[1] Criswell and Sack suggest that in part, the pathogenesis of the eosinophilia-myalgia syndrome (EMS) could be related to an inhibition of interferon-gamma synthesis by tryptophan metabolites. Although we know of no one who has actually measured interferon gamma in this illness, there is considerable indirect evidence that interferon gamma and cell-mediated immunity are turned on in EMS. Data presented at the conference on the eosinophilia-myalgia syndrome in Los Alamos, New Mexico, in June 1990, as well as those published by Silver and colleagues,[2] show elevated serum levels of kynurenine, quinolinic acid, neopterin, and β_2-microglobulin with reduced levels of serum tryptophan. This pattern suggests an augmentation of the indoleamine-2,3-dioxygenase (IDO) enzyme system in macrophages (which is stimulated by interferon gamma)[3] and it mimics the picture seen

in cancer patients who have been treated with exogenous interferon gamma or interleukin 2.[4] The latter is a cytokine which produces significant eosinophilia.[5] Thus, in all likelihood the abnormal tryptophan metabolism seen in EMS patients is a consequence of the immune activation in this disease rather than the cause of it. Indeed, one might reason that an important factor in the pathogenesis of EMS may be an excess, rather than a deficit of interferon gamma. The observed active catabolism of tryptophan by the IDO pathway may well lead to a deficiency of tryptophan and serotonin. If serotonin does play a role in down-regulating interferon production as suggested,[6] this deficit of serotonin may lead to an unchecked increase in interferon gamma and result in excessive activation of macrophages and eosinophils as seen in EMS.

In addition, although tryptophan metabolism may play a role in the pathogenesis of EMS, epidemiologic studies point increasingly to a contaminant as the principal causal factor.[7-9] The recent identification of the chemical structure of one such contaminant[10] may soon lead to animal and in vitro models which will permit dissection of this most interesting syndrome.

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Drs Criswell and Sack Respond

To THE EDITOR: We are pleased to respond to the thoughtful comments of Drs Hertzman and Brown. No one has measured interferon-gamma (IFN-γ) levels in patients with the eosinophilia-myalgia syndrome (EMS); thus, the finding by Silver and co-workers of elevated serum levels of L-kynurenine and quinolinic acid in such persons is unexplained.[1]

Interferon gamma can indeed stimulate indoleamine-2,3-dioxygenase (IDO), the rate limiting enzyme of the kynurenine pathway of L-tryptophan metabolism, but other substances such as endotoxin can also induce this enzyme. Furthermore, L-tryptophan influences the ability of IFN-γ to induce IDO.

Products of the indoleamine pathway of L-tryptophan metabolism, serotonin and melatonin, inhibit the production of IFN-γ. This may be important in the pathogenesis of EMS because IFN-γ is known to inhibit synthesis of collagen, the production of interleukins 4 and 5, and the production of IgE by B lymphocytes.[2-5]

It is likely that most, if not all, of the current cases of EMS are associated with a contaminant generated during the manufacturing of L-tryptophan. The manner in which L-tryptophan or a contaminant induces EMS is still open to speculation, however.

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